Citation:

Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz GA, Rosner B, Spiegelman D, Willett WC. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst.* 2004 Nov 3; 96 (21): 1,577-1,584.

PubMed ID: 15523086

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the association between fruit and vegetable consumption and risk of major chronic diseases in two large cohorts of men and women, followed up for more than a decade.

Inclusion Criteria:

- Nurses Health Study (NHS) participants: Nurses aged 30-55 years recruited in 1976
- Health Professionals' Follow-Up Study (HPFS) participants: Health professionals aged 40-75 years recruited in 1986.

Exclusion Criteria:

- Participants who reported daily energy intake outside the plausible range or who left 70 or more dietary questions blank at baseline
- Participants who reported cancer, diabetes, myocardial infarction, angina, stroke, and other heart diseases before 1984 for women and 1986 for men.

Description of Study Protocol:

Recruitment

NHS and HPFS participants.

Design

Prospective cohort study.

Dietary Intake/Dietary Assessment Methodology

Semi-quantitative food-frequency questionnaire (FFQ):

- Participants reported their average frequency of intake of the specified standard serving/portion size for each food over the past year
- The frequencies were reported in nine categories, ranging from less than once a month to six or more times per day.

Blinding Used

Study investigators reviewed medical records without knowing the participants' risk factor status.

Intervention

Not applicable.

Statistical Analysis

- Person-time of follow-up was contributed by each eligible participant from the date of return of the baseline FFQ to the diagnosis of cardiovascular disease (CVD), cancer, death, or the end of the studies, whichever came first
- For each two-year follow-up period in which events were reported, the intake for each composite item was computed as a cumulative average from all available FFQs up to the start of the follow-up period
- Cox proportional hazards models with time-dependent were used to examine the association between fruit and vegetable intake and risk of major chronic disease
- Participants were grouped into equal-sized quintiles of fruit and vegetable intake using the updated cumulative average. For each outcome, the relative risks (RR) were calculated by dividing the incidence among participants in each quintile by that in the lowest quintile.
- Linear relationships were also assessed using the median values of intake for deciles to minimize the influence of outliers.

Data Collection Summary:

Timing of Measurements

- The baseline dietary assessment was in 1984 for the NHS and 1986 for the HPFS
- Additional mailed questionnaires were completed in 1986, 1990, and 1994 for the NHS and 1990 and 1994 for the HPFS
- Study end dates were May 31, 1998 for the NHS and January 31, 1998 for the HPFS.

Dependent Variables

- Major chronic disease, defined as CVD, cancer (except nonmelanoma skin cancer, in situ breast cancer, and organ-confirmed prostate cancer), or non-traumatic death, whichever came first
- Cardiovascular disease was defined as fatal or non-fatal myocardial infarction and fatal or non-fatal stroke. Myocardial infarction was confirmed based on the WHO criteria. Stroke was confirmed if there was a typical neurologic defect of sudden or rapid onset lasting 24 hours or more that was attributed to a cerebrovascular event.

Independent Variables

Fruit and vegetable intake per day.

Control Variables

- Total calorie intake
- Age
- Smoking status
- Alcohol intake
- Body mass index (BMI)
- Multivitamin and vitamin E supplement use
- Physical activity
- Family history of myocardial infarction
- Family history of colon cancer
- Personal history of hypertension (HTN)
- Personal history of hypercholesterolemia
- Personal history of diabetes and (for women)
    - Family history of breast cancer
    - Menopausal status
    - History of hormone replacement therapy (HRT).

Description of Actual Data Sample:

- *Initial N:* 121,700 women and 51,529 men in the original cohorts
- *Attrition (final N):*
    - 71,910 women
    - 37,725 men
- *Age:* At study recruitment
    - Women: 30-55 years
    - Men: 40-75 years
- *Ethnicity:* Not reported
- *Other relevant demographics:* High socioeconomic populations
- *Anthropometrics:* None
- *Location:* US.

Summary of Results:

Key Findings

- Compared with participants in the lowest quintile of total fruit and vegetable consumption, participants in higher quintiles had slightly lower risks of major chronic diseases. Pooled multivariable adjusted relative risks (RR) for highest vs. lowest quintiles were 0.95 (95% CI: 0.89, 1.01) for all fruits and vegetables (P for trend=0.07), 0.95 (95% CI: 0.90, 1.01) for all fruits, (P for trend=0.18), and 0.96 (95% CI: 0.90, 1.01) for all vegetable (P for trend=0.13)
- Of the specific food groups, only green leafy vegetables showed a statistically significant association with lower risk among participants in the highest quintile compared to the lowers (RR=0.94, 95% CI: 0.89, 0.99; P for trend=0.01)
- The linear analyses also showed no association between consumption of fruits and vegetables and cancer incidence. Leafy green vegetables showed a significant inverse association with the risk of major chronic disease
- For CVD, the pooled RR in the continuous analysis was statistically significant. RR of CVD

was 0.88 (95% CI: 0.81, 0.95) for an increment of five servings per day of total fruits and vegetables; 0.87 (95% CI: 0.80, 0.94) and 0.93 (95% CI: 0.86, 1.00) for increments of three servings per day of all fruits and all vegetables, respectively; and 0.89 (95% CI: 0.83, 0.96) and 0.94 (95% CI: 0.91, 0.98) for increments of one serving per day of green leafy vegetables and of vitamin C-rich fruits and vegetables, respectively
- Higher fruit and vegetable intake showed a statistically significant inverse association with CVD disease (RR for at least eight vs. less than 1.5 servings per day was 0.70 (95% CI: 0.55, 0.89; P=0.0003).

Author Conclusion:

High consumption of fruits and vegetables, especially of green leafy vegetables, is associated with a small reduction in risk of major chronic disease. This risk reduction was due primarily to a lower incidence of CVD.

Reviewer Comments:

Strengths

- *Large, prospective cohorts*
- *Exposure and risk factors updated throughout study*
- *Outcomes verified by medical records and pathology reports*
- *Adjusted for many covariates.*

Weaknesses

- *Because cancer is a multistage process that takes place over several decades, a longer study period may have been needed for detecting the association between fruit and vegetable intake and changes in the early development of cancer*
- *Analyses based on overall fruit and vegetable intake may not be sufficiently specific to detect associations between cancer and a specific dietary factor*
- *The use of vitamin supplements and intake of fortified foods by the participants in the study might attenuate an effect of fruit and vegetable intake on the incidence of cancers if the nutrients in these supplements are associated with reduced cancer risk*
- *The homogeneity of socioeconomic status among the populations might limit the variation in the amount of fruit and vegetable intake (but also reduce bias from unmeasured confounders)*
- *Fruit and vegetable intake may have been overestimated because of the relatively large number of questions assessing these foods.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes

2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	N/A
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	N/A
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	N/A
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	???
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	???
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes